Low Dose Cytokines & Growth Factors in the Treatment of Skin Diseases

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DISCLOSURE OF RELEVANT RELATIONSHIPS WITH INDUSTRY 2017

- President World Health Academy Publishing House, Zurich, CH
- Editor, Dermatologic Therapy, Wiley-Blackwell
- Chief Medical Officer, BIOSKIN EVOLUTION®
- Consultant, SIGMA Shanghai, China - 2013
- Consultant, EVLaser
- Consultant, GLG, USA
- Consultant, Advance Medical, USA
- Consultant GUNA International, Italy & USA
- Scientific Director, Dolce Aqua®, Italy
- Consultant, CLINUVEL, Australia
- Chief Medical Officer, Applied Biology, Inc, Irvine, CA, USA
- Executive, Vitiligo Research Foundation, USA
- Editor in Chief, Journal of Pigmentary Disorders, 2014
The surprising link between **INFLAMMATION** and HEART ATTACKS, CANCER, SKIN DISEASES, ALZHEIMER’S and all other diseases is under investigation. **Low Dose Cytokines & Growth Factors** deserve a special place in the fight against the **SECRET KILLER**
INFLAMMATION

THE SECRET KILLER

The surprising link between INFLAMMATION and HEART ATTACKS, CANCER, ALZHEIMER’S and other diseases

What you can do to fight it
Inflammation (from Latin *inflammatio*) is part of the complex biological response of body tissues to harmful stimuli, such as pathogens, damaged cells, or irritants, and is a protective response involving immune cells, blood vessels, and molecular mediators. The function of inflammation is to eliminate the initial cause of cell injury, clear out necrotic cells and tissues damaged from the original insult and the inflammatory process, and to initiate tissue repair.
The classical signs of inflammation are heat, pain, redness, swelling, and loss of function. Inflammation is a generic response, and therefore it is considered as a mechanism of innate immunity, as compared to adaptive immunity, which is specific for each pathogen. Too little inflammation could lead to progressive tissue destruction by the harmful stimulus (e.g. bacteria) and compromise the survival of the organism. In contrast, chronic inflammation may lead to a host of diseases, such as hay fever, periodontitis, atherosclerosis, rheumatoid arthritis, and even cancer (e.g., gallbladder carcinoma). Inflammation is therefore normally closely regulated by the body.
Inflammation can be classified as either **acute or chronic**. Acute inflammation is the initial response of the body to harmful stimuli and is achieved by the increased movement of plasma and leukocytes (especially granulocytes) from the blood into the injured tissues. A series of biochemical events propagates and matures the inflammatory response, involving the local vascular system, the immune system, and various cells within the injured tissue.

**Prolonged inflammation**, known as **chronic inflammation**, leads to a progressive shift in the type of cells present at the site of inflammation, such as mononuclear cells, and is characterized by simultaneous destruction and healing of the tissue from the inflammatory process.
Can the brain inhibit inflammation generated in the skin? The lesson of gamma-melanocyte-stimulating hormone.


Abstract
The neuro-immuno-cutaneous-endocrine network is not a simple construct featuring organ systems intimately involved in the bridge between body and mind. **Mind-body influences are bi-directional and the skin should be considered an active neuroimmunoendocrine interface, where effector molecules of neuropeptides act as common words used in a dynamic dialogue between brain, immune system and skin.** Gamma-melanocyte stimulating hormone (gamma-MSH), one of the principal neuroimmunomodulating peptides, seems to exercise some control on the cutaneous inflammatory process, through a central action mediated by descending anti-inflammatory neural pathways and via local direct influence on inflammatory cells infiltrating the dermis, such as monocytes, macrophages and neutrophils. Gamma-MSH down-regulates the production of proinflammatory cytokines, while the production of the anti-inflammatory cytokine IL-10 is stimulated by gamma-MSH. Finally, gamma-MSH seems to regulate the expression of surface molecules in immunocompetent cells. Thus, further studies may lead to the use of **gamma-MSH as an important anti-inflammatory agent in clinical dermatology.**
Review

Can the brain inhibit inflammation generated in the skin? The lesson of α-melanocyte-stimulating hormone

Torello Lotti, MD, Beatrice Bianchi, PhD, Ilaria Ghersetich, MD, Benedetta Brazzini, MD, and Jana Hercogova, MD
Figure 1 In the brain α-melanocyte stimulating hormone is synthesized predominantly in the pituitary gland. When administered into the cerebral ventriculi (in mice) α-MSH inhibits the cutaneous inflammation induced by application of topical irritants and intradermal injection of cytokines. This action is related to the integrity of the spinal cord descending neurogenic pathways and of β2 receptors in the periphery. α-melanocyte stimulating hormone is also released in the plasma by the pituitary gland and by different cells, including keratinocytes, melanocytes, monocytes, macrophages, endothelial cells, adipocytes, fibroblasts and mast cells. Membrane receptors for α-MSH are present both in the brain and on nearly all the cells that produce and release α-MSH and participate in cutaneous inflammation mainly by reducing and terminating the same flogistic reactions.
Autoimmune markers in vitiligo patients appear correlated with obsession and phobia

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†Department of Critical Care Medicine and Surgery, Division of Dermatology, University of Florence, Florence, Italy
‡Department of Psychiatry, University of Florence, Florence, Italy
§Department of Emergency Medicine Research, Carolinas Medical Center, Charlotte, NC, USA

Figure 1 Psychological discomfort factors and social aspects shown in the graph are significantly higher in autoimmune markers vs. negative autoimmune markers vitiligo patients.
Components of Acute and Chronic Inflammatory responses
Chronic Inflammation is always entangled with Growth Factors, Cytokines, Neuropeptides, Hormones and Neuro-hormones


Rivkina T, Hercogova J, Lotti T.
What is a Growth Factor?

- A **growth factor** is a naturally occurring substance capable of stimulating **cellular growth**, proliferation, healing, and **cellular differentiation**. Usually it is a **protein** or a **steroid hormone**. Growth factors are important for regulating a variety of cellular processes.

- Growth factors typically act as signaling molecules between cells. Examples are **cytokines** and **hormones** that bind to specific **receptors** on the surface of their target **cells**.

- They often promote cell differentiation and maturation, which varies between growth factors. For example, **bone morphogenetic proteins** stimulate bone cell differentiation, while **fibroblast growth factors** and **vascular endothelial growth factors** stimulate blood vessel differentiation (angiogenesis).
Growth Factors are signalling molecules: Cytokines and Hormones
What is a Cytokine?

- **Cytokines** (*cyto*, from Greek "κύτταρο" *kyttaro* "cell" + *kines*, from Greek "κίνηση" *kinisi* "movement") are a broad and loose category of small proteins (~5–20 kDa) that are important in cell signaling.

- Their release has an effect on the behavior of cells around them. It can be said that cytokines are involved in autocrine signalling, paracrine signalling and endocrine signalling as immunomodulating agents.
Relationship between hormones and cytokines

FEMALE SEXUAL HORMONES

\[ \text{stimulate} \quad + \quad \text{Th}_1 \]
\[ \text{inhibit} \quad - \quad \text{Th}_2 \]

CORTISOL

\[ \text{inhibits} \quad - \quad \text{Th}_1 \]
\[ \text{stimulates} \quad + \quad \text{Th}_2 \]
17β-estradiol protects human skin fibroblasts and keratinocytes against oxidative damage.

Bottai G & Lotti T.


Our experimental data show that the presence of 17β-estradiol may protect skin cells against oxidative damage and that the dramatic lowering of oestrogen levels during menopause, could render skin more susceptible to oxidative damage.
Relationship between cytokines and hormones

IL-6

↑ CRH

↑ ACTH

↑ CORTISOL

↓ TSH

↓ TRH

↑ Somatostatin

TNF-α

IL-1β
AGEING = INFLAMMAGEING

AGING

Activation of immune cells

Senescence SAPS

TLRs

NFk B activation

Pro-inflammatory molecules

Macrophages

Granulocytes

Endothelial cells

Fibroblasts

Epithelial cells
Single cytokines and INFLAMMAGEING
...in low grade chronic inflammation

- TNF-α
- IL-6
- IL-8

Th1
Th17

Th2
TReg

Modificata a fini didattici (vedi freccia).
How to down-regulate IL-6?
DERMATOLOGY

Psycho-neuro-endocrine-immunology and low dose cytokines therapy: principles and evidences for an innovative medical approach in acute and chronic inflammatory diseases.

Abstract
The development of the Psycho-Neuro-Endocrine-Immunology (P.N.E.I.), induced a fundamental paradigm shift in the interpretation of the biological functions of the body; from a separatist point of view to an unifying one, centered on the recognized importance of the cross-talk between cells, organs and systems. This interplay is regulated by a great number of messenger molecules and their circulating levels are key parameters for the definition of both physiological and pathological conditions; indeed, the pathological phenomenon can be described as an imbalance in intercellular signaling. The restoration of the impaired signalling molecules balance is the goal of Low Dose Medicine (LDM), a new medical approach based on the administration of low physiological doses of messenger molecules (which act as homeostatic modulating agents). The validity of the Low Dose Medicine conceptual approach in terms of efficacy and safety is assessed by five years of scientific research in this field. In particular the role of low dose Sequential Kinetic Activation (SKA) signalling molecules oral administration in inflammatory status management is demonstrated.
Developing Th subsets **cross-regulate** expansion and functions each other.

Cooke, A. Th17 in Inflammatory Conditions. *2006, Rev Diabetic Stud 3: 72-7*
- Bettelli E. et al. Th17: the third member of the effector T cell trilogy. *Current Opinion in Immunology 2007, 19: 652-657*
Inflammation Cytokines
• TNF-α
• IL-6
• IL-8

ANTI-Inflammation Cytokines
• IL-4
• IL-10
• TGF-β

RECOVERING THE BALANCE IN SKIN INFLAMMAGEING
The neuro-immuno-cutaneous-endocrine network: relationship between mind and skin

Benedetta Brazzini,* Ilaria Ghersetich,* Jana Hercogova,† & Torello Lotti*

*Department of Dermoscience, University of Florence, Florence, Italy, and
†Department of Dermatology, Charles University, Prague, Czech Republic
LOW DOSE MEDICINE
FROM ITALIAN RESEARCH
AN INNOVATIVE
IMMUNOTHERAPEUTIC
APPROACH FOR SKIN DISORDERS

P.N.E.I. and Low Dose Cytokines
and Growth Factors Therapy

Torello Lotti
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Director of the Center for Interdisciplinary Studies of Regenerative Sciences, University of Rome
“Guglielmo Marconi” Rome, Italy; Director Institute of Dermatology LifeCrones, Florence, Italy;
President World Health Academy Foundation, Zurich, Switzerland.
Treating skin diseases according to the low dose medicine principles. Data and hypotheses.


Authors
Lotti T¹, Hercogova J², Wollina U³, Chokoeva AA⁴, Zarrab Z⁵, Gianfaldoni S⁶, Roccia MG⁷, Fioranelli M⁸, Tchernev G⁴.

Abstract
Cytokines, hormones and growth factors, also defined with the collective name of “signaling molecules” are key regulating agents of physiological (and also pathological) functions according to the principles of Psycho-Neuro-Endocrine-Immunology (P.N.E.I.). From the latest evidences in the fields of Molecular Biology, P.N.E.I. and nano-concentration, a new medical approach surfaces: the Low Dose Medicine (LDM), a new tool for the study and the design of therapeutic strategies based on immune rebalance interventions. LDM suggest the use of low-doses of activated signaling molecules in order to restore P.N.E.I. homeostatic conditions and an increasing number of scientific evidences of LDM approach efficacy and safety support LDM-based therapeutic approach for the treatment of many dermatological diseases such as Psoriasis Vulgaris, Vitiligo and Atopic Dermatitis.
Microinflammation and Neurogenic Inflammation: a clou in anti-ageing treatments

Neuropeptides in skin.
Lotti T, Hautmann G, Panconesi E.

Neuropeptides: role in inflammatory skin diseases.
Luger TA, Lotti T.

Neuropeptides and skin disorders. The new frontiers of neuro-endocrine-cutaneous immunology.
Lotti T, Bianchi B, Panconesi E.

The role of neuropeptides in the control of regional immunity.
Lotti T, D'Erme AM, Hercogová J.
Low Dose Medicine integrates state of the art scientific advances in:

- Psycho-Neuro-Endocrine-Immunology (PNEI)
- Molecular Biology
- Quantum Physics
DISEASE

HYPER-CONCENTRATION

10^{-6}

HEALTH

PHYSIOLOGICAL CONCENTRATION

10^{-15}

HYPO-CONCENTRATION

DISEASE
LOW DOSE MEDICINE

Low Dose Medicine integrates state of the art scientific advances in:

- Psycho-Neuro-Endocrine-Immunology (PNEI)
- Molecular Biology
- Quantum Physics

P.N.E.I.  Molecular Biology  Quantum Physics
LOW DOSE MEDICINE
A NOVEL, INTEGRATED, SYSTEMIC APPROACH TO DISEASES

BIO-REGULATING PHYSIOLOGY

LOW DOSE CYTOKINES
LOW DOSE GROWTH FACTORS
LOW DOSE HORMONES
LOW DOSE NEURO PEPTIDES
HOMEOSTATIC Control Systems and bi-directional cross-talk

CENTRAL NERVOUS SYSTEM & AUTONOMIC SYSTEM

ENDOCRINE SYSTEM

IMMUNE SYSTEM

DEFINITIONS

\[ g \text{ (gram)} = 1 \]

\[ 10^{-1} = 0.1 \]

\[ 10^{-2} = 0.01 \]

\[ \text{mg (milligram)} = 10^{-3} = 0.001 \]

\[ \mu\text{g (microgram)} = 10^{-6} = 0.000001 \]

\[ \text{ng (nanogram)} = 10^{-9} = 0.000000001 \]

\[ \text{pcg (picogram)} = 10^{-12} = 0.000000000001 \]

\[ \text{fg (femtogram)} = 10^{-15} = 0.000000000000001 \]
To compensate for decreased levels of a neurotransmitter like serotonin, the brain increases the number of receptors for that specific neurotransmitter.
The membrane receptor plays a KEY role.

ONLY physiological concentrations are able to activate or reactivate the membrane receptors and consequently, stimulate the physiological function of a target cell.


Th-1/Th-2 BALANCE

**Th1 UP-REGULATION**
- Th1
- Th17

**Th2 DOWN-REGULATION**
- Crohn’s Disease
- Psoriasis
- Vitiligo
- AGEING

**Th2 UP-REGULATION**
- Th2

**Th1 DOWN-REGULATION**
- Th1 TReg

**Asthma**
- Atopy
Cytokines UP
- IL-1
- IL-6
- TNF-α
- IL-17
- INF-γ
- IL-2
- IL-8

Physiological concentration
- IL-1
- IL-6
- TNF-α
- IL-17
- INF-γ
- IL-2
- IL-8

Cytokines DOWN
- TGF-β
- IL-4
- IL-10

Physiological concentration
- TGF-β
- IL-4
- IL-10

HYPER

HEALTH

HYPO
Neither good nor bad in Nature

Is it possible to modulate the action of cytokines and other signaling molecules in Low Grade Chronic Inflammation treatments?
The concept of **BALANCE** and the use of SKA low dose cytokines

Antagonistic cytokines are utilized in order to slow down a biological effect; **Same cytokines** in order to enhance a biological function.
THE CONCEPT OF BALANCE – RECIPROCITY of TH CELLS

Th0

IL-12 UP-REGULATES

Th1

Inflammatory diseases
IL-12, INF-γ

IL-4 UP-REGULATES

Th2

Allergy
IL-4

IL-4 DOWN-REGULATES

INF-γ DOWN-REGULATES

Th subsets cross-regulate expansion and functions each other.

- Cooke, A. Th17 in Inflammatory Conditions. 2006, Rev Diabetic Stud 3: 72-7
# Prescriptions According to the Aetiological Decisional Process

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Strengthening</th>
<th>Modulation</th>
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<tbody>
<tr>
<td>GCSF</td>
<td>GCSF 4C</td>
<td>IL-10 4C/IL-4 4C</td>
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<tr>
<td>INF alpha/gamma</td>
<td>INF alpha/gamma 4C</td>
<td>IL-4 4C</td>
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<td>Guna Anti IL-1 4C/IL-10 4C</td>
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<td>IL-2 4C</td>
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<td>INF-gamma 4C/IL-12 4C</td>
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<td>IL-10 4C/TGF-β1 4C</td>
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<td>IL-8</td>
<td>IL-8 4C</td>
<td>IL-10 4C/TGF-β1 4C</td>
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</tr>
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<td>IL-12 4C</td>
<td>IL-4 4C/IL-10 4C</td>
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<tr>
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<td>TGF-beta 4C</td>
<td>IL-12 4C</td>
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<tr>
<td>TNF</td>
<td>TNF-alpha 4C</td>
<td>Guna Anti IL-1 4C+IL-10 4C</td>
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DEFINITIONS

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Th-1/Th-2 BALANCE

Th1 UP-REGULATION

Th1 Th17

Crohn’s Disease
Psoriasis
Vitiligo
AGEING

Th2 DOWN-REGULATION

... 

Th2 UP-REGULATION

Th2

Asthma
Atopy
...

Th1 DOWN-REGULATION

Th1 TReg
Webster Marketon JI, Glaser R. Cell Immunol, 2008; 252 (1-2):16-26
Heterologous bio-mimetic growth factors in anti-aging treatments: biological selectivity, indications, side effects and complication

**Daily Treatment**

- GUNA ANTI IL/-1 (4CH, 20+20 Drops)
- GUNA INTERLEUKIN 10 (4CH, 20+20 Drops)
- GUNA Platelet derived Growth Factor (4CH, 20+20 Drops)
- GUNA FGF (4CH, 20+20 Drops)
- GUNA IGF (4CH, 20+20 Drops)
Daily Treatment

- GUNA ANTI IL/-1 (4CH, 20+20 Drops)
- GUNA INTERLEUKIN 10 (4CH, 20+20 Drops)
- GUNA Platelet derived Growth Factor (4CH, 20+20 Drops)
- GUNA FGF (4CH, 20+20 Drops)
- GUNA IGF (4CH, 20+20 Drops)
IL-1 family is a group of 11 cytokines, which induces a complex network of proinflammatory cytokines and via expression of integrins on leukocytes and endothelial cells, regulates and initiates inflammatory responses.

IL-1α and IL-1β are the most studied members, because they were discovered first and because they possess strongly proinflammatory effect. They have a natural antagonist IL-1Ra (IL-1 receptor antagonist). All three of them include a beta trefoil fold and bind IL-1 receptor (IL-1R) and activate signaling via MyD88 adaptor, which is described in the Signaling section of this page. IL-1Ra regulates IL-1α and IL-1β proinflammatory activity by competing with them for binding sites of the receptor.
Daily Treatment

- GUNA ANTI IL/-1 (4CH, 20+20 Drops)
- GUNA INTERLEUKIN 10 (4CH, 20+20 Drops)
- GUNA Platelet derived Growth Factor (4CH, 20+20 Drops)
- GUNA FGF (4CH, 20+20 Drops)
- GUNA IGF (4CH, 20+20 Drops)
Interleukin 10 (IL-10), also known as human cytokine synthesis inhibitory factor (CSIF), is an anti-inflammatory cytokine. In humans, interleukin 10 is encoded by the IL10 gene. IL-10 signals through a receptor complex consisting of two IL-10 receptor-1 and two IL-10 receptor 2 proteins. Consequently, the functional receptor consists of four IL-10 receptor molecules. IL-10 binding induces STAT3 signaling via the phosphorylation of the cytoplasmic tails of IL-10 receptor 1 + IL-10 receptor 2 by JAK1 and Tyk2 respectively.
Daily Treatment

- GUNA ANTI IL/-1 (4CH, 20+20 Drops)
- GUNA INTERLEUKIN 10 (4CH, 20+20 Drops)
- GUNA Platelet derived Growth Factor (4CH, 20+20 Drops)
- GUNA FGF (4CH, 20+20 Drops)
- GUNA IGF (4CH, 20+20 Drops)
Platelet-derived growth factor (PDGF) is one of the numerous growth factors, or proteins that regulate cell growth and division. In particular, it plays a significant role in blood vessel formation (angiogenesis), the growth of blood vessels from already-existing blood vessel tissue. Uncontrolled angiogenesis is a characteristic of cancer. In chemical terms, platelet-derived growth factor is a dimeric glycoprotein composed of two A (-AA) or two B (-BB) chains or a combination of the two (-AB).

PDGF is a potent mitogen for cells of mesenchymal origin, including fibroblasts, smooth muscle cells and glial cells. In both mouse and human, the PDGF signalling network consists of four ligands, PDGFA-D, and two receptors, PDGFRalpha and PDGFRbeta. All PDGFs function as secreted, disulphide-linked homodimers, but only PDGFA and B can form functional heterodimers.
Daily Treatment

- GUNA ANTI IL/-1  (4CH, 20+20 Drops)
- GUNA INTERLEUKIN 10 (4CH, 20+20 Drops)
- GUNA Platelet derived Growth Factor (4CH, 20+20 Drops)
- GUNA FGF  (4CH, 20+20 Drops)
- GUNA IGF  (4CH, 20+20 Drops)
Fibroblast growth factors, or FGFs, are a family of growth factors, with members involved in angiogenesis, wound healing, embryonic development and various endocrine signaling pathways. The FGFs are heparin-binding proteins and interactions with cell-surface-associated heparan sulfate proteoglycans have been shown to be essential for FGF signal transduction. FGFs are key players in the processes of proliferation and differentiation of wide variety of cells and tissues.
Heterologous bio-mimetic growth factors in anti-aging treatments: biological selectivity, indications, side effects and complication

Daily Treatment

- GUNA ANTI IL/-1  (4CH, 20+20 Drops)
- GUNA INTERLEUKIN 10 (4CH, 20+20 Drops)
- GUNA Platelet derived Growth Factor (4CH, 20+20 Drops)
- GUNA FGF  (4CH, 20+20 Drops)
- GUNA IGF  (4CH, 20+20 Drops)
Somatomedins are produced, predominantly by the liver, when growth hormones act on target tissue. Somatomedins inhibit the release of growth hormones by acting directly on anterior pituitary and by stimulating the secretion of somatostatin from the hypothalamus.

Somatomedins are a group of hormones that promote cell growth and division in response to stimulation by growth hormone (GH) also known as somatotropin (STH).
Heterologous bio-mimetic growth factors in anti-aging treatments: biological selectivity, HIGH indications, microinflammation, side effects, NONE, and complication, NONE.
OBESITY INDUCED INFLAMMATION

http://www.my-personaltrainer.it/dimagrire/adipochine.html
Obesity, psoriasis, and microbiota: an unexplored dangerous connection?


Roccia MG, Fioranelli M, Lotti T.
IL-6 increases in healthy subjects after 50 years of life and reaches high levels in advanced old age. The physiological increase of IL-6 is a consequence of an effective adaptation to stressors.

Low Grade Chronic Inflammation correlated to metabolic syndrome and/or other pathologies induces a shift in the curve of aging with a reduction of life span.
Increased mitochondrial function

Improvement of skin self-renewal functions

Reduction of the inflammatory response

Peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1alpha

GUNA-MELATONI

SIRT1

IMPROVEMENT OF SKIN SELF-RENEWAL FUNCTIONS

INCREASING MITOCHONDRIAL FUNCTION

STAT 6

NF-kB

NUCLEAR ACTIVATION

REDUCTION OF THE INFLAMMATORY RESPONSE
SIRT1 regulates MAPK pathways in the skin: insight into the molecular pathways of cell survival.


Becatti M1, Fiorillo C, Barygina V, Cecchi C, Lotti T
Thanks for your attention!